ACCU-BREAK'S INNOVATIVE TABLET TECHNOLOGY – 2016 ADVANCEMENTS

Here, David Beach, PhD, Technical Consultant, Formulation Development and Manufacturing, Accu-Break Pharmaceuticals, provides a run-down of the company's tablet technologies which, among other benefits, allow patients to split tablets readily and reliably.

Tablet splitting as a means to manage costs, swallowing, titration and dose adjustment could be a better and more efficient alternative if it were easier and less risky.

For example, Accu-Break Pharmaceuticals has developed two worldwide patented distinct multi layer tablet technologies, known as Accu-B and Accu-T, which incorporate a drug-free layer.

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ACCU-B

With the Accu-B technology, the dosage form has two layers, one of which is drug free. The second layer contains drug and is deeply scored (see Figure 1). The drug-free layer provides several unique features: first and foremost, given the deep score in the drug layer, the drug-free layer forms a backbone that gives the finished dosage form mechanical strength to withstand packaging and shipping operations. Secondly, the drug-free layer is the fracture plane for the Accu-B tablet. The tablet can be broken through the score and the fracture occurs in the drug-free layer.

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Using the Accu-B technology, scored tablets can be made that completely satisfy the testing and data requirements for both the European Pharmacopoeia's Monograph 0478 and the US FDA's 2013 Guidance for Industry, "Tablet Scoring: Nomenclature, Labeling, and Data Evaluation".

The FDA Guidance is intended to:

- Reduce potential risks associated with inaccurate doses resulting from tablet splitting due to uneven drug content, loss of mass, weight variation and/or stability changes
- Ensure consistent scoring, pattern and function between innovator drugs and generic copies
- Allow for "functional scoring" to be included in the product label for Sponsors supplying requisite supporting data.

> "Unique fixed-dose combination tablets can be made where the top and bottom layers contain different actives. In this configuration, the two different drug layers can be separated if desired by splitting the tablet through the middle-drug free layer."

ACCU-T

The Accu-T technology allows for five layers in a taller-than-wide tablet, and the incorporation of drug-free layers to serve one of two purposes.

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One is that the drug-free layer provides a physical barrier between active ingredients. This barrier allows the formulation of incompatible actives with no worries about co-mixing and resultant physical or chemical stability issues. The technology utilises machinery that can produce tablets with up to five compressed layers so the use of more than one drug-free layer can facilitate a "poly pill" with three different API-containing formulations separated by inert/placebo layers.

In the other application, a drug-free breaking layer is incorporated into the middle of an Accu-T tablet and can be used to separate the drug-containing layers. Since the drug-containing layers are physically located at the top and bottom of this taller-than-wide tablet, breaking the tablet through the middle drug-free layer separates the dose into exact halves. The top and bottom layers might contain the same active (Figure 2). Or unique fixed-dose combination (FDC) tablets can be made where the top and bottom layers contain different actives. In this configuration, the two different drug layers can be separated if desired by splitting the tablet through the middle-drug free layer (Figure 3).

Patients taking antihypertensive FDCs, for example, can be confronted with side effects that result from one of the drugs within the FDC, resulting in at best, poor compliance and in many instances prescription discontinuation. With the Accu-T FDC tablet design, a patient could suspend treatment with one of the drugs in the FDC by simply breaking the tablet through the middle drug-free layer. When appropriate, the patient could then resume taking the whole tablet, which allows some dose flexibility without having to stop the prescription entirely.

The tablet could also be used to initiate treatment with a single agent and then add the second therapeutic agent and, thus, efficiently transitioning the patient into a convenient FDC without the need for separate prescriptions during the titration phase.

WHY HAVE FDCS BEEN CRITICISED IN THE PAST?

The largest historical criticism of FDCs has come from the lack of dose flexibility. Taking antihypertensive FDCs as an example, treatment is typically initiated with a single agent, which is titrated to a maximum tolerated dose. If the desired effect on lowering blood pressure is not achieved, a second agent is added, which also requires titration and can lead to lowering the dose of the first agent. A third agent is sometimes added to the mix, or substituted for one of the initial drugs. This process continues until the patient's blood pressure is within the target range, and then the physician looks for an option to transition the patient to an FDC that contains APIs at the effective dose for that patient. This is done of course to simplify the dosing regimen for the patient in an attempt to maintain adherence to the regimen.

Problems arise when a dose adjustment is necessary due to the inflexibility of traditional FDCs. The convenience of a single dosage form is offset by the inability to manage dose adjustments without the need for new prescriptions. If a patient is transitioned to an FDC, inevitably an adjustment will be made to their dose(s), their regimen, the specific drugs being used, or all of the above. So, from that perspective, the criticism is justified. However, for those patients who are effectively managed using FDCs, the ability to take lower doses of two or more medications in a single dosage form is highly desired, especially if it is a once-a-day regimen.

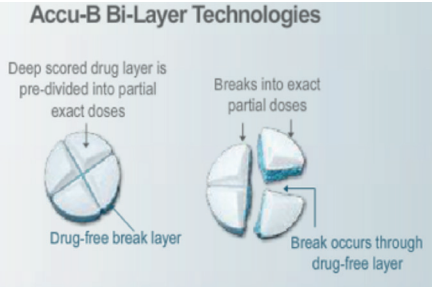

Figure 1: The Accu-B bilayer tablet technology.

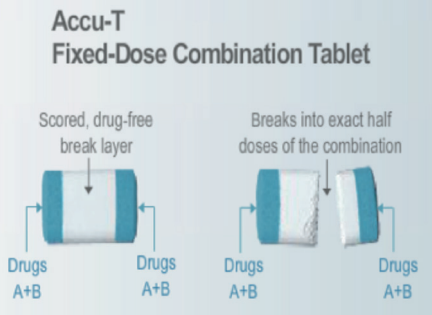

Figure 2: The Accu-T technology configured for a fixed-dose combination.

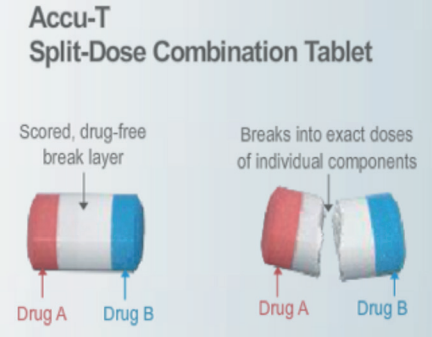

Figure 3: The Accu-T technology configured for a split-dose combination.

FURTHER APPLICATIONS OF ACCU-B

Exploration of the Accu-B type technology for extended-, modified- and sustained-release tablets has produced product with the same release profile as the intact, whole tablet. In the case of a modified-release dosage form, the engineering of the tablet tooling and thus the finished, compressed tablet, is crucial to maintaining the desirable drug release profile. As the deep score of the Accu-B tablet reduces the surface area of the rupture of the active layer when the tablet is broken, achievement of identical release profiles becomes a simple formulation modification of the existing tablet, and in many cases can obviate the need for bioequivalence testing of the Accu-Break dosage form based on identical *in vitro* release profiles. This attribute makes the adoption of the Accu-Break technology attractive for those sponsors seeking patent life extension along with all of the other desirable attributes of the Accu-Break technology portfolio.

ABOUT ACCU-BREAK

Based in Hollywood, FL, US, Accu-Break Pharmaceuticals is a technology licensing and product development company. The company has invented, developed and patented a suite of novel Accu-Break technologies that enable pharmaceutical tablets to be made that can be subdivided by hand into accurate partial doses with the intent of making it easier and safer for patients to adjust their dose. Behind the strength of its innovative inventions and broad patent portfolio, the company is currently developing its first product, and is licensing the Accu-Break technologies to other parties for product development. Accu-Break currently has 58 patents issued and four patents pending worldwide.